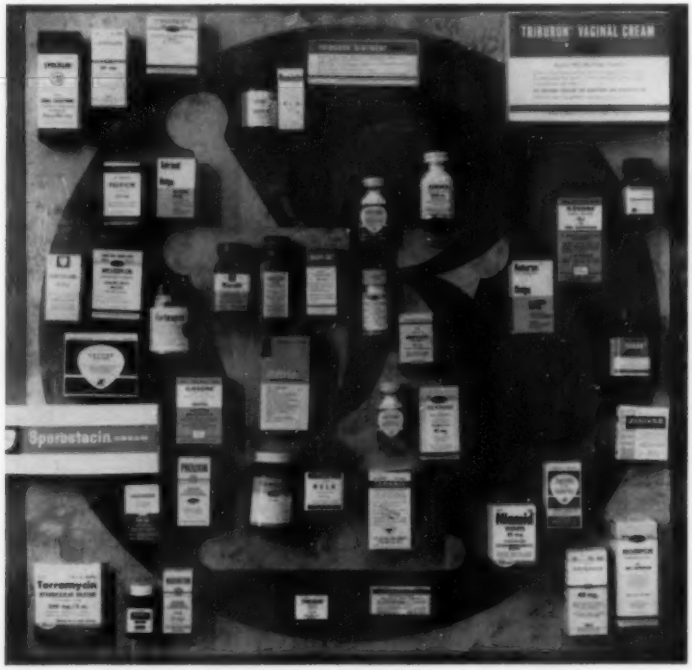
American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



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E D I T O R I A L

DRUG RESEARCH TODAY

THE large number of new medicinals released during 1959 is evidence of the almost feverish activity in drug research. Such research is spurred on to an ever-increasing tempo by the intense competition between the many companies comprising the drug industry.

Critics of the drug industry who claim that there is no such competition today would soon change their opinion if they could observe the almost frenetic lives of research executives who know full well that company position and even survival depends on new and better drugs, and these quickly.

Other critics voice their displeasure that not all of the new drugs released each year are major breakthroughs as were drugs like penicillin, cortisone, and chlorothiazide. To expect such major accomplishments from each program of drug research is completely unrealistic. Furthermore, the improvement of some already existing drug by a therapeutic margin of say ten to twenty per cent may spell the difference between success and failure in treating many patients. Is there anyone, for example, who considers cortisone as good as prednisone or the latter in turn as good as dexamethasone? Should we have ceased all sulfonamide research with the development of sulfapyridine or sulfathiazole? It must be remembered that in setting up a research program no one has, or can have, the assurance of a ringing success. A project even after long and costly pursuit may result in something with only possible superiority. Even this often cannot be established for a certainty until it has been used on thousands of patients in an objective clinical appraisal. Only too often, early clinical enthusiasm gives way to the sad conclusion that the new drug is not quite what was hoped. These are the risks that must be taken and the costs that must be written off—costs which are often staggering.

The question frequently arises whether the industry, the health professions, and the public at large are benefited by the present head-

long pace of pharmaceutical research, much of it unrewarding. Those who say that the achievements do not justify the expense and that the resulting multiplication of products is wasteful fail to understand certain basic facts concerning research and the free enterprise system. In the first place, just who is there in industry, in government, or elsewhere who could predict just what research should be undertaken and invariably be right? As the situation now exists, many capable men match wits on this with the certain knowledge that good judgment and lots of luck will pay off. Those who believe in some other system just do not believe in free enterprise, which is the system in which Americans profess to believe.

Secondly, just where in the world can our critics point to a better, more productive system? Russia? England? Where, other than in America and some few countries whose economic system is patterned after our own, are today's miracle drugs more widely available, the professions free, and the health of the people given greater care and attention? Those who would tamper with our free and smoothly functioning system of drug research and distribution should reflect on what the inevitable result of such tampering would be. Some of our critics seem as naive as a child who is surprised that the clock he has "fixed" won't run. Others, we suspect, subscribe to the philosophy of Marx and Lenin but hide it behind a facade of alleged concern for the people. Thinking Americans should not be misled by such phony liberalism. We have much that needs correcting in this country if we are to survive. Let us not tamper with one of our towers of strength for which we are known and respected the world over. As it has been so aptly stated elsewhere, "There is no missile-gap in the drug industry." Neither will there be as long as private initiative and freedom from unreasonable restraint continues as our national policy toward the industry.

L. F. Tice

NEW DRUGS OF 1959

By L. F. Tice *

The rapid pace of pharmaceutical research and the increasing importance attached to new medicinal agents makes an understanding of new drugs imperative for both pharmacist and physician. It is the purpose of this review to assist those in the health professions with the task of keeping up to date on the many new and important therapeutic agents released during 1959. While some few drugs still under clinical investigation are mentioned, most of those considered in this review were released for distribution during 1959.

Anti-Infectives

IN the field of antibiotics, a number of modifications and improvements have been made in some of the well-known antibiotics and, in addition, several newly isolated antibiotics have been reported.

The possibility of preparing synthetic penicillins by the appropriate treatment of 6-aminopenicillanic acid was announced about a year ago. Since then, over 500 such derivatives have been prepared. Of these, the best so far seems to be 6-(α-phenoxypropionamido)-penicillanic acid. This differs from penicillin G only in being an α-phenoxyethyl derivative instead of a benzyl and, from penicillin V, in being an α-phenoxyethyl derivative instead of a phenoxymethyl; i.e., it is a homologue of penicillin V. It is used as the potassium salt and, like penicillin V, it is not readily destroyed by gastric acidity. When given orally, it is even better absorbed than penicillin V and is believed to be more effective in its antibacterial action. Its antibacterial spectrum is the same as that of other penicillins. Alpha-phenoxyethyl penicillin is available in this country as Syncillin

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(Bristol), Chemipen (Squibb), and Maxipen (Pfizer). In England, it is available as Broxil (Beecham Laboratories). This new synthetic penicillin is supplied as 125 and 250 mg. tablets and as a powder. The dose is 250 mg., three to six times daily. It should not be given to persons known to be sensitive to other penicillins.

While demethylchlortetracycline (DMCT) was reported in 1958, considerable clinical experience with it during 1959 has firmly established it among the tetracyclines. Demethylchlortetracycline differs from chlortetracycline (Aureomycin—Lederle) only in lacking a methyl group at position 6 on the naphthacene ring. This difference, however, makes it more resistant to both acid and alkali degradation and reduces the incidence of gastrointestinal disturbances. Most important is the fact that it is cleared by the kidneys more slowly, resulting in prolonged blood levels. Demethylchlortetracycline is available as 150 mg. capsules (Declomycin—Lederle) and also as a product for suspension and pediatric drops. The usual oral dose is 600 mg. daily divided into two or four doses.

The parenteral use of tetracycline has always been somewhat complicated by the difficulty of preparing a solution well tolerated by tissue. A new much more soluble form of tetracycline is its N^2-1-pyrrolidinomethyl derivative (Syntetrin—Bristol; Velacycline—Squibb). This new compound has the pyrrolidinomethyl attached to the amide nitrogen at position 2. It is claimed to be 2500 times as soluble in body fluids as tetracycline itself. It is supplied in dry-filled ampuls for I.M. or I.V. use. The product for intramuscular use also contains the local anesthetic, lidocaine. The I.V. product, after being restored with pyrogen-free water, is further diluted with normal saline or isotonic dextrose before slow intravenous infusion.

An improved preconstituted solution of oxytetracycline for intramuscular injection (Terramycin I.M.—Pfizer) was released during 1959. It consists of a solution of an ethanolammonium magnesium salt of oxytetracycline and is made by reacting oxytetracycline, a magnesium salt, and an alkanolamine in a propylene glycol-water vehicle. The local anesthetic, lidocaine, and an antoxidant are also added to the product. This solution is stable if protected from air and is claimed to be well-tolerated causing very little tissue irritation following injection.

The preparation of the propionic ester of erythromycin as a means of protecting the drug against gastric acidity and improving

its absorption was an important development in 1958. This ester (Ilosone—Lilly), however, is sufficiently soluble in aqueous liquids to make a pediatric suspension unpleasant in taste. Recently, this problem was solved by forming the lauryl sulfate salt of the propionic ester. In this, the basic dimethyl amine group of the erythromycin molecule is involved in the formation of a poorly soluble salt with lauryl sulfuric acid. It is supplied as flavored granules for the preparation of an oral suspension (Ilosone Lauryl Sulfate 125 for Oral Suspension—Lilly) which, when the proper amount of water is added, contains the equivalent of 125 mg. of erythromycin base/5 cc. It is also supplied in another form (Ilosone Lauryl Sulfate Drops—Lilly) which, when diluted with water, contains 5 mg./drop, using a special dropper as provided.

Griseofulvin, introduced in 1958, continued to gain clinical acceptance in 1959. It seems to be the best therapy so far developed for the most troublesome fungus infections of the skin and its appendages such as tinea capitis and onychomycosis. In the case of the latter, it is the only therapy ever developed offering much promise of success. Griseofulvin is available in 250 mg. tablets as Grifulvin (McNeil) and Fulvicin (Schering). It is also supplied under its generic name by Ayerst Laboratories.

A number of new antibiotics were announced during 1959. Some of the more important ones were fervenulin, streptozotocin, aspartocin, rifomycin B, humatin, colistin, tylosin, and thiostrepton. Fervenulin was reported by Upjohn workers to be an effective anti-trichomonal drug. It is obtained from *S. fervens*. Streptozotocin is obtained from *S. achromogenes* var. 128. It has shown good activity against both gram-positive and gram-negative organisms and it is of interest since no cross resistance to it has been found with organisms that are resistant to most other antibiotics. It is effective both orally and parenterally.

Aspartocin was described by Lederle scientists as derived from *S. griselus* var. *spiralis*. Its name is based on its high content of aspartic acid. It has been found effective against many resistant strains of staphylococci and streptococci. Rifomycin B is produced by *S. mediterranei* and it is currently being studied in Italy. It is said to be effective against both gram-positive organisms and mycobacteria and to have low toxicity. It is, however, poorly absorbed when given orally and it causes tissue irritation when injected intramuscularly.

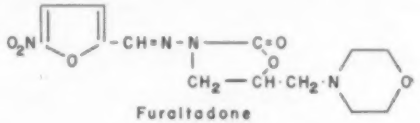
Humatin is under clinical investigations sponsored by Parke, Davis & Co. It seems particularly useful in the treatment of diarrheas whether of amebic or bacillary origin. It is given orally and is not absorbed into the bloodstream. A course of treatment usually requires five days but marked symptomatic relief often occurs within two days.

Colistin is being studied by Warner-Chilcott although it was originally reported by Japanese workers. In many respects, it is similar to polymyxin. For oral use, it is employed as the sulfate (Coly-mycin S—Warner-Chilcott) while, for parenteral use, the sodium methane-sulfonate is employed (Coly-mycin M). It is effective chiefly against gram-negative organisms and it is reported to have given excellent results when given orally in the treatment of infant diarrheas.

Tylosin is a new antibiotic discovered at Eli Lilly & Co. and isolated from a strain of *S. fradiae*. It is effective against gram-positive organisms and some that are gram-negative. So far, it has shown promise in preventing certain respiratory diseases in poultry and to stimulate weight gain when fed to swine and poultry. In acid solution, tylosin splits off a molecule of mycarose forming desmycosin which has equal antibacterial action.

Thiostrepton is another antibiotic recommended principally for veterinary use. It is effective in treating bovine mastitis and provides a means of treatment avoiding the use of penicillin. Penicillin residues in milk are believed harmful because of their sensitizing potential. Thiostrepton is available as Gargon (Squibb).

Any new antibacterial agent which is neither a sulfonamide nor an antibiotic is certain to be of interest, particularly if it can be used for systemic infections. Such is the case with the new nitrofuran derivative, Furaltadone (Altafur—Eaton). This chem-



Furaltadone
ALTAFUR

ically is 5-morpholinomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidinone. Furaltadone, when given orally, is effective against a wide

variety of gram-positive and gram-negative organisms including most strains of staphylococci. Based on experience with other nitrofurans, resistance to the drug is not believed likely to develop even when used for a long period of time. The average adult dose is 250 mg. four times a day, preferably at meal time. So far, the only side effects which have occurred in some few patients are nausea and vomiting. The possibility of a blood dyscrasia exists but it is not presently thought likely. Furaltadone is supplied in 250 mg. tablets.

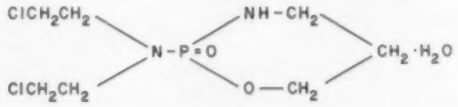
Another synthetic having useful antibacterial properties is the bis-quaternary compound, triclobisonium chloride (Triburon—Roche). Chemically, it is N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyl]-N,N′-dimethyl-1,6-hexanediamine bis-methochloride. It also has antitrichomonal and antimonilial action and, therefore, is particularly suitable for use in vaginitis. It is supplied as a 0.1 per cent cream for intravaginal use and also as an ointment with and without hydrocortisone for dermatologic use.

A new anti-fungal agent, chlordantoin, is marketed in the form of a cream for intravaginal use (Sporostacin Cream—Ortho). Chemically, chlordantoin is 5-(1-ethylamyl)-3-trichloromethylthiohydantoin. It is effective against various fungi including *Candida albicans*. Against the latter, it is effective in a concentration of only 1:300,000 at pH 7.0 and even more effective at pH 4.5. It is not effective against the protozoan, *Trichomonas vaginalis*, but it does have some antibacterial action.

Chlordantoin is stable, non-toxic, and non-staining. The product, Sporostacin Cream (Ortho), contains 1 per cent of this as the active ingredient.

Anti-Neoplastic Agents

A new drug related to the nitrogen mustards is the product cyclophosphamide (Cytoxan—Mead Johnson). This is also known



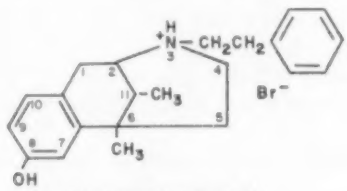
Cyclophosphamide
CYTOXAN

overseas as Endoxan. Chemically, it is 2H-1,3,2-oxazaphosphorine-2-[bis-(2-chloroethyl) amino]-tetrahydro-2-oxide. The use of this compound depends upon the *in vivo* rupture of the phosphorus nitrogen bond by the action of phosphamidases. This permits the ionization of the chlorines in the chloroethyl groups producing an active alkylating agent. Phosphamidases have been shown to occur in malignant tissues in higher amounts than in normal tissue and, for this reason, such a compound may prove more toxic to the cells of neoplasms than to other body cells. Cyclophosphamide has proven useful both in hematologic malignancies and solid tumors, in some cases causing prolonged remissions. Like all such cytotoxic agents, however, it cannot be expected to effect "cures".

Another drug but one acting as an anti-folic acid compound is A-Methopterin (Methotrexate—Lederle). This is 4-amino-N^{10} methyl pteroyl glutamic acid. It is indicated in the treatment of acute leukemia in children. In adults, toxic reactions usually occur before any therapeutic response can be achieved. This close relative of aminopterin is both less active and less toxic, and this is believed to make possible a more precise dosage regimen. As with other folic acid antimetabolites, overdosage can be controlled by using Leucovorin as an antidote.

Analgesics

The new potent analgesic announced by the National Institutes of Health in 1958 (NIH-7519) has been widely tested and is now commercially available. It is known as phenazocine bromide (Prin-

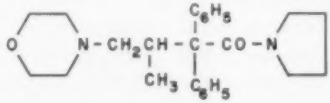


Phenazocine Bromide
NIH-7519
PRINADOL

adol—Smith Kline and French). Chemically, it is 1,2,3,4,5,6-hexahydro-8-hydroxy-6, 11-dimethyl-3-phenethyl-2,6-methano-3-benzazo-

cine hydrobromide. Early clinical results indicate that phenazocine bromide is a somewhat more potent analgesic than morphine and that it causes less respiratory depression, hypotension, nausea, and vomiting. It also causes less sedation so that its analgesic action should not be judged on this basis. Phenazocine is given in a dose of 2 mg. intramuscularly with the 24-hour dose usually not more than 12 mg. It is supplied in 1 cc. ampuls and 10 cc. vials containing 2 mg./cc.

A methadone-like analgesic, dextromoramide, recently was marketed as Palfium (G. F. Harvey). This is *d*-1-(3-methyl-2,2-diphenyl-



Dextromoramide
PALFIUM

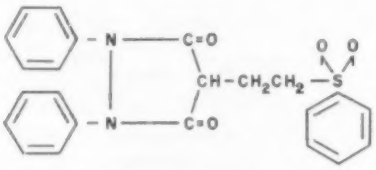
4-morpholinobutyryl)pyrrolidine tartrate. This compound was first synthesized by P. A. Janssen and has been under clinical study since 1956. It is claimed to be more potent than morphine and to be less addictive. The usual dose is 5 mg. orally or by injection.

Two new analgesics of the salicylate group are calcium acetylsalicylate carbamide (Calurin—Smith Dorsey) and choline salicylate. The latter is supplied in two forms: Arthropan Liquid and Actasal Pediatric Drops (Purdue Frederick). Calurin is a freely soluble, stable calcium-aspirin-carbamide complex which, because of its rapid solubility, minimizes gastric irritation and produces therapeutic salicylate blood levels in a very short time. It has been shown by several workers that the more rapidly aspirin dissolves in the stomach the less likely gastric irritation and intolerance. Calurin is supplied in the form of flavored tablets containing the equivalent of 300 mg. of aspirin.

Choline salicylate appears also to be rapidly absorbed and, in the two products mentioned, absorption is claimed to take place five times as rapidly as with regular aspirin. Arthropan Liquid contains 870 mg. of choline salicylate per 5 ml. equivalent to 0.6 Gm. of aspirin. Actasal Pediatric Drops contain 104.5 mg./0.6 ml. of choline salicylate (also equal to 0.6 Gm. of aspirin per 5 ml.).

Uricosuric Agent

The uricosuric action of phenylbutazone is well-known but it is too weak in promoting uric acid excretion to be useful for this purpose. A closely related compound, sulfinpyrazone (Anturan—Geigy), is



Sulfinpyrazone
ANTURAN

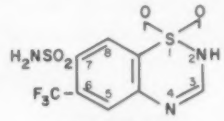
now available which is a very potent uricosuric agent. Chemically, it is 1,2-diphenyl-4-(2'-phenylsulfinethyl)3,5-pyrazolidinedione. It differs from phenylbutazone only in having a phenylsulfinethyl at position 4 on the pyrazolidine ring instead of a butyl group. Sulfinpyrazone, like other uricosuric agents, acts by blocking the tubular resorption of urates. Since its half-life is only 3 hours (phenylbutazone, 3 days), it must be given in divided doses throughout the day. Salicylates and citrates antagonize its action and are contraindicated. If an analgesic is required, phenylbutazone may be given concomitantly.

The dose of sulfinpyrazone is 50 mg. four times daily—with meals and with milk at bedtime. This is gradually increased to a maintenance dose which varies up to 800 mg. a day. Side effects include gastric disturbance and, occasionally, a drug rash. Unlike phenylbutazone, it does not cause sodium retention. So far, no proven instance of a blood dyscrasia has been recorded but, since it is a close relative of some drugs which have been known to cause agranulocytosis, the possibility of such an event must not be dismissed. Sulfinpyrazine is supplied as Anturan in scored 100 mg. tablets.

Diuretics

The enthusiastic clinical acceptance of chlorothiazide and its dihydro derivative resulted in intensive research efforts to synthesize related substances that might be superior. A number of diuretic-

antihypertensives in this class were released last year. The potentiation of certain medicinals by the introduction of a trifluoromethyl group has been observed as, for example, in the phenothiazine class of psychotherapeutic agents. This same approach was tried in the field of diuretics and the drug, flumethiazide (Ademol—Squibb), is

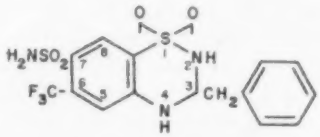


Flumethiazide
ADEMOL

chlorothiazide with the chlorine at position 6 replaced with a trifluoromethyl group. Its chemical name is 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. Flumethiazide seems to be only about equal in potency to chlorothiazide but it is claimed to cause less potassium loss. It is available as 500 mg. tablets.

The dihydro derivative of flumethiazide (Saluron—Bristol) was also released last year. It differs only in having a single bond between the carbon at position 3 and the nitrogen at position 4. It has about the same potency as dihydrochlorothiazide but is claimed to cause less potassium loss. It is available as 50 mg. tablets and as a syrup containing 50 mg./5 cc.

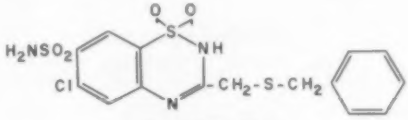
Still greater potentiation of the compound is seen in benzydroflumethiazide (Naturetin—Squibb). This has a benzyl substituent at



NATURETIN

position 3 in addition to the removal of the double bond, and its chemical name is 3-benzyl-3,4-dihydro-6-trifluoromethyl-7-sulfonamide-1,2,4-benzothiadiazine-1,1-dioxide. It is claimed to have 100 times the potency of chlorothiazide and is available in 2.5 and 5 mg. tablets.

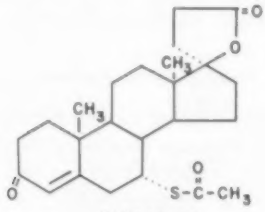
Still another is under clinical trial; namely, Benzthiazide (Pfizer). This is 3-benzylthiomethyl-6-chloro-7-sulfonamide-1,2,4-benzothiadiazine-1,1-dioxide.



Benzthiazide

While many of the chlorothiazide analogs are much more potent on a mg. to mg. basis, it is not fully established whether they are clinically superior. The very small dosage required of some may in itself make flexibility in dosage hard to achieve.

An entirely different class of diuretics is seen in the aldosterone antagonists. Aldosterone is the naturally occurring adrenal corticosteroid believed to be the most important among those regulating the fluid-electrolyte balance of the body. A number of compounds known as the spirolactones have been found to antagonize the action of aldosterone and, by so doing, cause diuresis. Spirolactones are steroids having a carbon in ring D (carbon 17) common with the lactone ring. The first spirolactone to be marketed is spironolactone (Aldac-

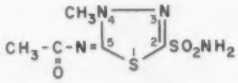


Aldactone
SC-9420

tone—Searle). This is 3-(3-oxo-7α-acetylthio-17β-hydroxy-4-androstene-17α-yl) propionic acid-γ-lactone. Aldosterone does not appear to affect glucocorticoid or pituitary activity and has no other known harmful effects. The onset of action is slow, unlike chlorothiazide, so that a maximum effect is not seen for three days. The average adult daily dose is 400 mg. in divided doses. In some few patients, as much as 1200 mg. daily may be needed. Both chlorothiazide and the mercurial diuretics potentiate it. Aldactone is supplied as 100 mg. tablets.

Drugs in Glaucoma

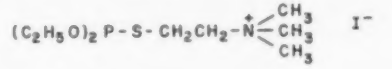
Three new drugs for use in the treatment of glaucoma are the carbonic anhydrase inhibitor, methazolamide (Neptazane—Lederle);



Methazolamide
NEPTAZANE

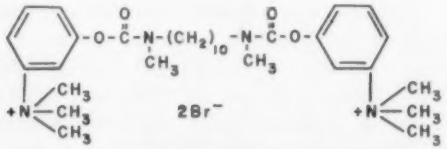
an organic thiophosphate (Phospholine Iodide—Campbell Products); and a bis-quaternary cholinergic (Humorsol—Merck Sharp & Dohme). Methazolamide is 5-acetylimino-4-methyl Δ^2-1,3,4-thiadiazoline-2-sulfonamide. It is chemically related to other carbonic anhydrase inhibitors and acts similarly in reducing the formation of aqueous fluid. Methazolamide is said to be effective in some cases in which acetazolamide (Diamox—Lederle) is not but it is not recommended as superior to acetazolamide in most cases. It is supplied in 50 mg. tablets.

Phospholine Iodide is [2-(diethoxyphosphinylthio)ethyl]-trimethyl ammonium iodide. It is a potent acetylcholinesterase inhibitor



Phospholine Iodide

acting in the eye as a powerful miotic and reducing intra-ocular pressure by providing better drainage of aqueous fluid. It is supplied as a dry powder in vials so that either a 0.125 per cent (5 cc.) or a 0.25 per cent (2.5 cc.) solution can be prepared. The solution is stable at room temperature for about 30 days. The bis-quaternary, demecarium bromide (Humorsol—Merck Sharp & Dohme), is a decameth-

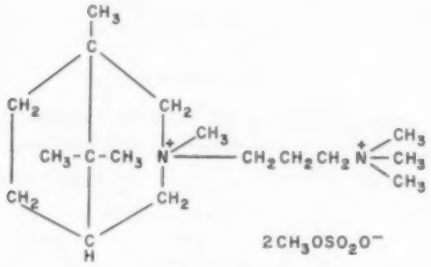


Decamarium Bromide
HUMORSOL

ylene bis-(*m*-dimethylaminophenyl-N-methyl carbamate) dimethobromide and acts as a potent cholinergic drug. It is supplied in 5 cc. dropper bottles containing a 0.25 per cent solution.

Antihypertensives

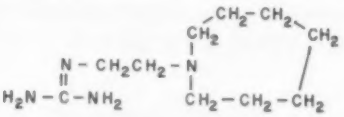
A new ganglionic blocking agent, trimethidinium methosulfate (Ostensin—Wyeth) was released in 1959. Chemically, it is *d*-[N-



Trimethidinium methosulfate
OSTENSIN

methyl-N-(γ-trimethylammonium propyl]-1-methyl-8,8-dimethyl-3-azabicyclo (3,2,1) octane dimethosulfate. As with other drugs in this class, the dose must be carefully regulated to accomplish the desired reduction in blood pressure without postural hypotension or excessive side effects. Absorption is best on a fasting stomach. It is supplied as 20 and 40 mg. tablets.

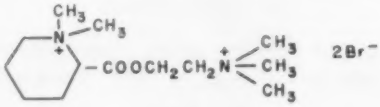
An antihypertensive acting by reducing the supply of endogenous nor-epinephrine is guanethidine (Ismelin—Ciba). Chemically, it is



SU-5864
GUANETHIDINE
ISMELIN

[2-(octahydro-1-azocinyl)-ethyl] guanidine. Ismelin is still on clinical trial.

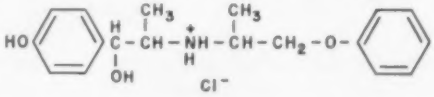
Another antihypertensive on clinical trial is JB-591 (Lakeside). This is β-dimethylaminoethyl-N-methylpipecolate dimethobromide. It appears to lower blood pressure by both a peripheral and a central action.



JB-591

Vasodilators

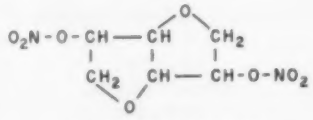
A new compound acting to relax the smooth muscle of the peripheral vascular system and the uterus is isoxsuprine hydrochloride (Vasodilan—Mead Johnson). It is 1-(*p*-hydroxyphenyl)-2-(1′-



Isoxsuprine HCl
VASODILAN

methyl-2′-phenoxyethylamino) propanol-1-hydrochloride. It is used to increase circulation in the peripheral vascular diseases, to increase cerebral blood flow, and also in the treatment of dysmenorrhea and threatened abortion. Dosage must be determined on the basis of condition being treated and patient response. It is available as 10 mg. tablets for oral use and as a parenteral solution 5 mg./cc. for I.M. use.

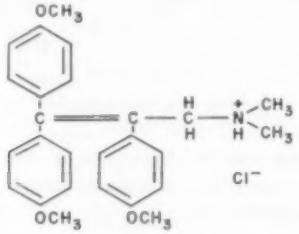
A new organic nitrate, isosorbide dinitrate (Isordil—Ives-Cameron), is claimed to be long-acting and to be useful as a coronary



Isosorbide Dinitrate
ISORDIL

vasodilator in angina. Its chemical name is 1,4 :3,6-dianhydrosorbitol 2,5-dinitrate. The average dose is one (10 mg.) tablet, one-half hour before meals and at bedtime but the dose should be adjusted (5-20 mg.) to the needs of the patient.

A new coronary vasodilator also having value in cardiac arrhythmias is under clinical testing. It is known generically as amotriphene (Myordil—Winthrop). Chemically, it is 3-dimethylamino-1,1,2-



MYORDIL

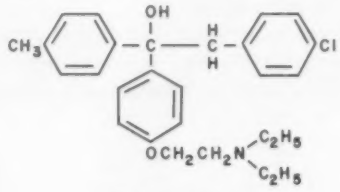
tris-(4-methoxyphenyl)-1-propene hydrochloride. Amotriphene has been reported as causing marked and definite improvement in a number of patients suffering with angina. It also has demonstrated considerable antifibrillatory activity. In dogs, for example, in which cardiac arrhythmias were produced with sublethal doses of digitalis, normal sinus rhythm was restored in most instances by its use. Toxic doses of the drug affect the central nervous system causing convulsions rather than affecting the heart.

Still another drug—in this case, a peripheral vasodilator—is the product, nylidrine hydrochloride (Arlidin—U. S. Vitamin). It is described as phenyl-2-butylnorsuprifen and claimed to greatly increase arterial blood flow in occlusive artery disease.

Hypocholesterolemic Agent

The search for some drug which will effectively lower blood cholesterol levels continues. A new drug in this category but still in the experimental stage is Triparanol (Merrell). This is 1-[*p*-(β-

diethylaminoethoxy)-phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl) ethanol. It is believed to depress serum cholesterol by its enzymatic inhibitory

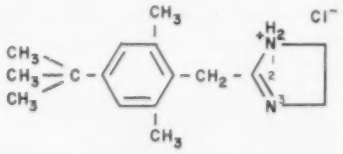


Triparanol
MER-29

action on the biosynthesis of cholesterol in the liver. Side effects reported are nausea, vomiting, and albuminuria but, as yet, no hepatic toxicity has been reported.

Vasoconstrictor

The well-known vasoconstrictor, naphazoline hydrochloride (Privine—Ciba), now has a closely related companion product also an imidazoline derivative. This new vasoconstrictor is known as xylometazoline hydrochloride (Otrivin—Ciba). Chemically, it is

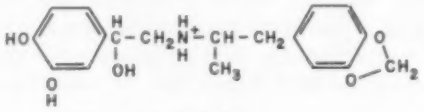


Xylometazoline HCl
OTRIVIN

2-(4-tert. butyl-2,6-dimethylbenzyl) imidazoline hydrochloride. It is claimed to be an effective, long-acting vasoconstrictor and decongestant, when applied topically in the nose, and not to cause stinging or irritation. Otrivin is supplied as both a nasal solution and a nasal spray in a concentration of both 0.1 per cent and 0.05 per cent. The latter is intended for pediatric use.

Bronchodilator

A new bronchodilator effective by all routes of administration is α-[(α-methyl-3,4-methylenedioxyphenethylamino)-methyl] protocatechuyl alcohol hydrochloride (Caytine—Lakeside). It is claimed

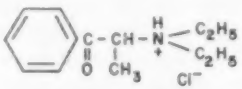


CAYTINE

not to raise blood pressure or cause any untoward effect on the heart, liver, or kidneys. Caytine is useful in asthma, emphysema, bronchiectasis, and bronchitis. It is supplied in the form of tablets (2 mg.), tablets with phenobarbital, an inhalation (1:100), and as an injection (0.5 mg./cc.). When given by injection or inhalation, it acts within minutes. Orally, its effect is seen after about 15 minutes and lasts about two hours.

New Anorexigenic

The use of drugs to depress the appetite is a common practice in many anti-obesity programs. Amphetamine, desoxyephedrine, and phenmetrazine are all widely used for this purpose. Stimulation of the central nervous system and cardiovascular effects with drugs of this type are often undesirable, particularly in those patients who may also have either heart disease or hypertension. Both amphetamine and desoxyephedrine are known to be somewhat hazardous in such patients, with phenmetrazine, much less so. A new anorexigenic claimed to have little CNS or cardiovascular action is diethylpropion (Tepanil—National Drug; Tenuate—Merrell). It is 1-phenyl-2-



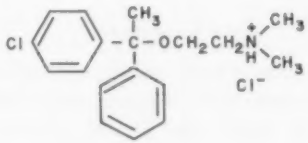
Diethylpropion
TEPANIL
TENUATE

diethylamino-propanone-1 hydrochloride. It is structurally related to the sympathomimetic amines but differs in having a ketone function and in having its amino nitrogen as a diethylamine.

Diethylpropion is said to depress the appetite effectively and, since it is not a stimulant, it can be given also in the evening to help avoid bedtime "snacks". Its only occasional side effect is dryness of the mouth by reason of its weak anticholinergic action. It is supplied in 25 mg. tablets—the dose being one tablet three times daily one hour before meals; a fourth may be taken in mid-evening if desired.

Anti-Parkinsonian Agent

While no drug is fully satisfactory in the treatment of Parkinson's disease and many new drugs for this condition are available, each new addition seems worthy of attention. During 1959, the drug, chlorphenoxamine hydrochloride (Phenoxene—Pitman-Moore), was re-

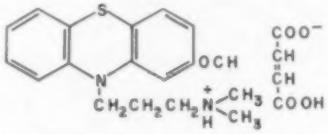


Chlorphenoxamine HCl
PHENOXENE

leased as a new addition in this field. Chlorphenoxamine hydrochloride is β-dimethylaminoethyl (*p*-chloro-α-methyl benzhydryl) ether hydrochloride. It is very closely related to the well-known antihistamine, diphenhydramine, which itself has had some success in the control of paralysis agitans. Chlorphenoxamine is said to be especially useful when rigidity and impairment of muscle contraction are the major difficulties. In the case of tremor, it is best to give it with other drugs since it is not very effective alone. One decided advantage is that it apparently can be given to patients with glaucoma. The dose is 50 mg., three times daily, with the maximum 100 mg., four times daily. Phenoxene is supplied in 50 mg. tablets.

Tranquilizers

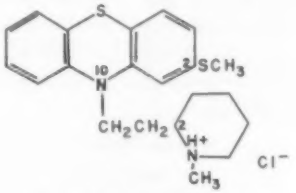
The phenothiazine group of psychotherapeutic agents continued to expand in 1959. Methoxypromazine maleate (Tentone—Lederle)



Methoxypromazine Maleate
TENTONE

is 2-methoxy-10-(3′-dimethylaminopropyl) phenothiazine maleate. It differs from chlorpromazine in having a methoxy group in place of a chlorine attached at position 2. It is one of the milder drugs in the phenothiazene group. As with all such drugs, the required dose varies widely depending on the patient and the condition treated. Tentone is supplied in 10, 25, and 50 mg. tablets.

Another drug in this category is thioridazine hydrochloride (Mellaril—Sandoz). This is 2-methylmercapto-10-[2-(N-methyl-

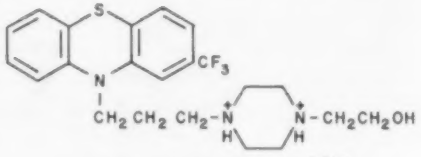


Thioridazine HCl
MELLARIL

2-piperidyl)-ethyl] phenothiazine hydrochloride. It is said not to produce extrapyramidal side effects (tremors) as do many of the phenothiazines. Mellaril is supplied in 10, 25, and 100 mg. tablets.

The potentiation of certain drugs by the introduction of a trifluoromethyl group has been mentioned previously. This principle has been applied in converting perphenazine (Trilafon—Schering) to Fluphenazine (Permitil—White; Prolixin—Squibb). Its chemical name is 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10 phenothiazyl)-propyl] piperazine dihydrochloride. Fluphenazine is a potent, long-

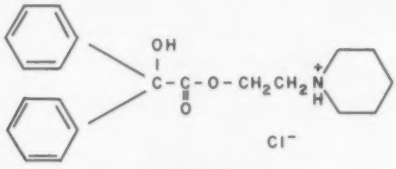
acting drug which is effective if given only once or twice a day. The dose depends upon the condition being treated. Since Permitil is recommended in the milder anxiety states, it is supplied as 0.25 mg.



Fluphenazine
PERMITIL
PROLIXIN

tablets. Prolixin, while it is the same drug, is intended for use in the more severe mental disorders and for frankly psychotic patients. It is supplied in 1.0, 2.5, and 5 mg. tablets.

A new tranquilizer related to the diphenylmethane group is piperilate hydrochloride (Sycotrol—Reed & Carnrick). This chem-



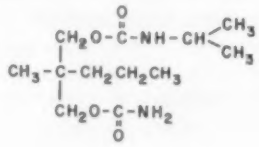
Piperilate HCl
SYCOTROL

ically is β-piperidinoethyl benzilate hydrochloride. It has both a tranquilizing and an anticholinergic action and is claimed particularly useful in patients with gastrointestinal or cardiac stress conditions accompanied by anxiety. It is supplied as 3 mg. tablets.

Muscle Relaxant

While meprobamate has some little muscle relaxing action, it is primarily a tranquilizer. An N-isopropyl derivative, carisoprodol (Soma—Wallace; Rela—Schering), has much greater activity as a muscle relaxant while still retaining its tranquilizing effects. Chem-

ically, carisoprodol is N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate. Carisoprodol relaxes abnormal tension of skeletal muscles by a selective blocking action on the interneurons and it also

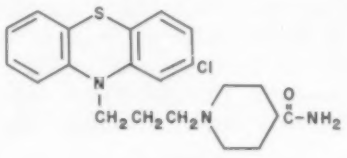


Carisoprodol
SOMA
RELA

seems to modify pain perception without affecting peripheral pain or withdrawal reflexes. Carisoprodol is indicated in bursitis, disc syndrome, fibromyositis, low back pain, sprains, stiff neck, and whiplash injury. The only side effect with high doses may be slight drowsiness. It is available as both Soma and Rela in 350 mg. tablets.

Anti-Emetics

Several of the antihistamines and tranquilizers have marked ability to control nausea and vomiting. A phenothiazine that is said to be a potent agent in controlling nausea, yet without marked tranquilizing action, is pipamazine (Mornidine—Searle). Chemically,

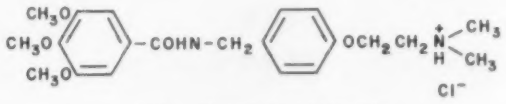


Pipamazine
MORNIDINE

it is 10-[3-(4-carbamoylpiperidino)propyl]-2-chlorophenothiazine. Pipamazine is believed to act on the emetic center in the medulla and it is recommended as a means of controlling nausea and vomiting as seen postoperatively, in pregnancy, and following intensive radiotherapy. In the usual therapeutic doses, pipamazine has not shown any toxicity to the liver or caused any blood dyscrasia or hypotension.

The usual dose of the drug is 5 mg. every four to six hours as needed. It is supplied in 5 mg. tablets and in ampuls containing 5 mg./cc. for intramuscular use.

Another anti-emetic drug for the prevention and control of nausea is trimethoxybenzamide hydrochloride (Tigan—Roche). This



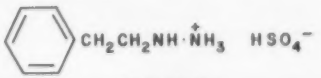
Trimethoxybenzamide HCl
TIGAN

is not a phenothiazine, its chemical name being 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride. It is said to have a specific effect on the chemoreceptor or trigger zone in the medulla through which impulses are conveyed to the vomiting center. It does not produce any noticeable side effects and no contraindications to its use are known. The oral and parenteral dose is 100 mg. and it is supplied in both 100 mg. tablets and ampuls containing 100 mg./cc.

Psychic Energizers

The more potent central stimulants in use today came into being as a result of the unusual properties of iproniazid. Whether their anti-depressive effect is due to their inhibition of monamine oxidase in the brain is not firmly established but many of these drugs can be demonstrated to have an inhibitory action on this enzyme.

The drug, phenelzine (Nardil—Warner-Chilcott), is a lower homologue of the Lakeside product, Catron, differing only in lacking a

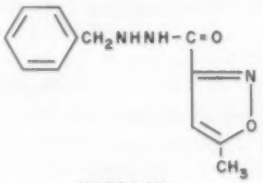


Phenelzine
NARDIL

methyl group on the alpha carbon. Its chemical name is β-phenethylhydrazine hydrogen sulfate. Phenelzine produces a response in the patient in a much shorter time than does iproniazid, requiring only

three to five days, and it also seems to pass the blood brain barrier more effectively. Like other related drugs, it is used in certain endogenous depression states. It is not as toxic as iproniazid although patients should be carefully watched for signs of liver damage. Side effects include postural hypotension, nausea, delayed micturition, and constipation. Dosage must be carefully regulated, with the initial dose being 15 mg., three times a day. After maximum benefit has been achieved (about one week), the dose is gradually reduced to the minimum consistent with maintenance of the patient's improved status. This may be as little as 15 mg. a day or less. Nardil is supplied as 15 mg. tablets.

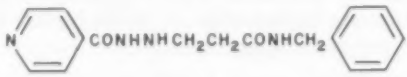
The drug, isocarboxazid (Marplan—Roche), is another hydrazine derivative recently introduced and superior in effectiveness



MARPLAN

and safety to iproniazid. Chemically, it is 1-benzyl-2-(5-methyl-3-isoxazolyl carbonyl) hydrazine. It is said to be thirty times as potent as iproniazid and superior to it in treating both depression states and relieving pain of angina. As with other drugs in this class, some little time is required for its full effect to be evident and then dosage can be reduced to a maintenance level. It is supplied in 10 mg. tablets.

Still another drug in this class is the product, nialamide (Niamid —Pfizer). This, like iproniazid, is an isonicotinyl hydrazide deriva-



Nialamid

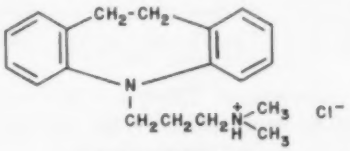
NIAMID

tive; its chemical name is 1-[2-(benzylcarbamyl) ethyl]-2-isonicotinyl hydrazine. Nialamide seems to be somewhat less toxic than other drugs in its class possibly because the compound is not split in the

body with the release of hydrazine fragments. It is supplied in 25 and 100 mg. tablets.

Several other hydrazine derivatives are on clinical trial including benzylpicolinyl hydrazine and serine isopropyl hydrazine.

A non-hydrazine central stimulant but one having considerable potency in treating depression states is imipramine hydrochloride (Tofrānil-Geigy). This is N-(3'-dimethylaminopropyl)-iminodi-



Imipramine HCl
TOFRĀNIL

benzyl hydrochloride. It does not inhibit monamine oxidase but it does relieve depression of endogenous origin and does so without marked euphoria or psychokinetic stimulation. Imipramine is administered either orally or intramuscularly in a dose which depends upon the patient and the condition under treatment. For outpatients, a dose of 75 mg. per day (divided) is suggested with a maximum of 200 mg. daily. Hospitalized patients may be given somewhat larger doses with a daily maximum of 300 mg. Once response is achieved, the maintenance dose is usually much smaller (50 mg. or less). Side effects are those of an anticholinergic and rarely tremor, sweating, dizziness, and skin rash. Hypotension may also occur. Tofrānil is supplied as 25 mg. tablets and in ampuls containing 25 mg./2 cc. for intramuscular use.

Another non-hydrazine but one being a potent monamine oxidase inhibitor is under clinical trial. It is SKF-385A and, chemically, is trans-*dl*-2-phenylcyclopropylamine.

Adrenal Steroids

Few new potent adrenal steroids were released in 1959, the drug dexamethasone being the most recent potent glucocorticoid made commercially available. Several modifications of existing steroids were introduced, however, wherein their suitability for certain uses

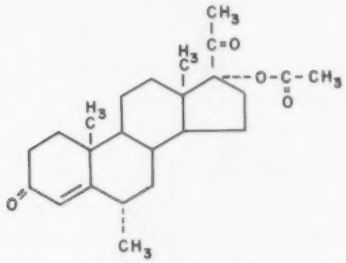
may have been improved. In addition, a new steroid specifically intended for topical use was released. The steroid, 6-methyl prednisolone (Medrol—Upjohn), as the 21-sodium succinate is supplied as Solu-Medrol (Upjohn). It is restored with water just prior to use. This succinic acid ester of the alcohol group at position 21, neutralized to give a monosodium salt, provides a convenient water-soluble compound. When Solu-Medrol is restored by adding the water provided as a diluent, it gives a buffered solution suitable either for intravenous injection or intrarectal instillation. By contrast, the 21-acetate being insoluble in water is used as a suspension and is contained in Depo-Medrol (Upjohn). This is an aqueous suspension (40 mg./cc.) containing, in addition to the 6-methylprednisolone-21-acetate, polyethylene glycol, sodium chloride, and a preservative. It can be used intramuscularly as a depot form, by intra-articular injection, by intrabursal injection, directly into a lesion, and intrarectally. When used intramuscularly, a single injection once a week will usually suffice.

Triamcinolone is 16-α-hydroxy-9α-fluoro-prednisolone. The acetonide involving the alcohol groups at positions 16 and 17 provides a lipophilic compound used topically in various products. The diacetate is also insoluble in water and makes possible an aqueous suspension either for oral use or for injection to provide a localized effect. For oral use, it is available as Aristocort Syrup (Lederle) and, for parenteral use, it is supplied as Aristocort Parenteral Triamcinolone Diacetate. The latter is used by intrasynovial, intra-articular, and subcutaneous injection where a prolonged and intense local effect is desired. Each cc. contains 25 mg. of the micronized diacetate.

A steroid specifically for topical use is fluorometholone (Oxylone —Upjohn). This is 21-desoxy-9α-fluoro-6α-methyl prednisolone. It is unique in that a methyl group replaces the primary alcohol group at position 21. Fluorometholone is claimed to have a local anti-inflammatory action forty times that of hydrocortisone while, orally, it is no more effective than hydrocortisone. Its high potency topically makes it possible to use very small amounts in dermatological products thus reducing the risk of systemic effects. It is supplied in two forms: Oxylone Cream 0.025 per cent (Upjohn) and Neo-Oxylone Ointment 0.025 per cent with neomycin sulfate and parabens, the latter as preservatives.

Progestin

A number of potent progestins have been released in recent years including norethindrone (Norlutin—Parke Davis) and norethynodrel (Enovid—Searle). This last year, still another was released; namely, medroxyprogesterone acetate (Provera—Upjohn). This product is

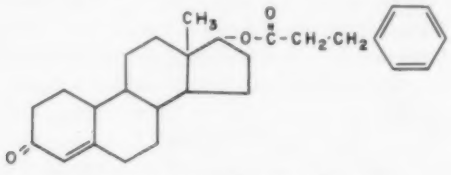


Medroxyprogesterone
Acetate
PROVERA

17-α-hydroxy-6α-methyl progesterone acetate and it reflects the potentiation of some steroids by a 6-α-methyl substituent. It is available in 2.5 and 10 mg. tablets.

Anabolic Steroid

The search for a potent anabolic steroid without marked androgenic activity continued during 1959. The absence of a methyl at position 19 greatly reduces androgenic activity. The latest of the 19-nor compounds is nandrolone phenpropionate (Durabolin—



Nandrolone Phenpropionate
DURABOLIN

Organon). This is 19-nor-Δ^4-androstene-17β-ol-3-one-β-phenylpropionate. It is claimed to be a potent anabolic agent encouraging tissue

repair and positive nitrogen balance. It is supplied in ampuls, each cc. containing 25 mg. of the steroid ester dissolved in sterile sesame oil. It is administered by intramuscular or subcutaneous injection once weekly, the adult dose being 25 mg.

Vitamins and Hematinics

While no new vitamins of importance have been announced in recent years, improvements in dosage forms continue to be developed.

A new depot form of B_{12} is seen in a zinc tannate complex of cyanocobalamin. This is marketed as Bevitam (Merrell) and Depinar (Armour). It is available in a multiple dose vial containing a mixture of crystalline cyanocobalamin and its zinc tannate complex, the mixture being in lyophilized form. The diluent supplied is normal saline. When restored, it provides a total of 500 mcg. of B_{12} per cc., part being in the readily absorbed soluble form but most as the slowly absorbed complex. It is claimed that, in this form, very little of the B_{12} is lost by urinary excretion, there being a gradual release and utilization of B_{12} lasting over a period of almost a month. The product is recommended both in the treatment of pernicious anemia, in geriatrics, and in cases where a high intake of B_{12} is indicated.

There is a considerable body of evidence to the effect that vitamin K_1 is superior to menadione and other K_1 analogs in treating hypoprothrombinemia, particularly when caused by excessive doses of the dicoumarol-type anticoagulants. Vitamin K_1 is also useful in all those clinical conditions accompanied by lowered blood prothrombin levels. While a natural K_1 has been available for some time, synthetic K_1 is now available both for oral and parenteral use (Konakion—Roche). Its "solubilized" form is made possible by the use of a surfactant. For oral use, 5 mg. capsules are available and, for intramuscular, subcutaneous, and slow intravenous use, it is available in 1 mg./0.5 cc., 10 mg./cc., and 25 mg./2.5 ampuls. The "solubilized" form makes it possible to administer the product by slow intravenous injection.

It is a well-known fact that large oral doses of the water-soluble vitamins are followed by their fairly rapid loss by urinary excretion, their chemical degradation, or both. A new sustained-release polyvitamin product (Fortespan—SKF) is designed to accomplish more efficient utilization of the essential vitamins. These capsules contain only the water-soluble vitamins in sustained-release form. The oil-

soluble vitamins while present need no such treatment since they are stored in body tissues and not rapidly utilized or excreted. A single capsule supplies several times the MDR of each vitamin, and it is recommended that the capsule be taken upon arising or at breakfast. A three-layered multivitamin tablet giving a three-stage release is also marketed as S. A. Vite (Ayerst).

The sustained-release approach is also seen in the field of hematinics in the case of a new ferrous sulfate product (Feosol Spansules—SKF). Here, the intent is to minimize or prevent the gastro-intestinal disturbances often caused by ferrous sulfate in its usual dosage forms. This product also makes possible a one dose a day regimen and requires only a fraction of the usual daily dose of ferrous sulfate for effective therapy. Each Feosol Spansule contains 150 mg. of ferrous sulfate.

Enzymes

During 1959, several new enzyme products were introduced as well as some new dosage forms of certain enzymes already in clinical use.

The most noteworthy new enzyme product is human fibrinolysin (Actase—Ortho). This is prepared from profibrinolysin separated from the globulin fraction of human plasma. It is converted to active fibrinolysin (also known as plasmin) by a highly purified streptokinase, the latter derived from cultures of a special strain of β-hemolytic streptococci. Fibrinolysin when injected has a preferential lytic action on fibrin and one which is much more specific than that of other proteolytic enzymes. It is strongly adsorbed to fibrin and this, in addition to the presence in the blood of an antiplasmin, results in only a very limited lytic action on proteins other than fibrin. Another marked advantage other than its specificity lies in the fact that it is a natural substance found in the blood unlike other proteolytic enzymes. Fibrinolysin is often life-saving in such conditions as venous thrombosis and pulmonary embolism and it is also a valuable therapeutic aid in other thromboembolitic difficulties. Anticoagulant therapy given concurrently does not appear to impair its effectiveness and is often desirable.

The only side effect so far noted with fibrinolysin has been a temperature rise, probably due to traces of foreign protein via the

streptokinase used or resulting from the lytic effect on the fibrin clot. Contraindications include any hemorrhagic diathesis, major liver dysfunction, and hypofibrinogenemia.

Actase is supplied in vials containing 50,000 units in lyophilized form. It is restored with 10 cc. of water for injection and then further diluted with 250 cc. of 5 per cent dextrose. It is administered intravenously over a period of two hours. The usual treatment consists of three such injections over a one to five day period for such conditions as thrombophlebitis or phlebothrombosis. In pulmonary embolism, 50,000-100,000 units are administered daily over a one to three day period depending upon the clinical response. Merck Sharp & Dohme is also reported as preparing to market fibrinolysin, their product now being under extensive clinical study.

Another new enzyme product now under clinical study is fibrinuclease (Elase—Parke Davis). This is a combination of fibrinolysin derived from bovine plasma and desoxyribonuclease from bovine pancreas. In combination, these cause the lysis of both the fibrin in exudates and the nuclear material present in pus. Such action not only promotes healing but it increases the efficacy of topically applied antibiotics.

The use of alpha-chymotrypsin as a preliminary step in cataract surgery has been described as a major advance. Alpha-chymotrypsin is obtained from bovine pancreas and, when purified, is a pure crystalline material. A solution of this enzyme is introduced following an incision of the cornea by the surgeon. The enzyme causes a rapid loosening of the zonules making the lens much more readily removed and reducing the risk of capsular rupture, loss of vitreous, and detachment of the retina. Only 2-4 minutes are required after instillation for the enzymatic action to take place.

Alpha-chymotrypsin for use in cataract surgery is supplied in lyophilized form. When reconstituted with diluent, it gives a solution containing a suitable dilution of the enzyme. It is available as Alpha Chymar (Armour) and Zolyse (Alcon Laboratories).

The use of enzymes such as streptokinase and trypsin for their anti-inflammatory action when injected has received considerable clinical endorsement. In more recent years, buccal tablets have been claimed to be effective and two such products are now available. These are Chymar Buccal (Armour) and Varidase Buccal (Lederle). Chymar is chymotrypsin and the buccal tablets contain 10,000 units.

Varidase is a mixture of streptokinase and streptodornase. In the case of the latter product, only the streptokinase exerts an anti-inflammatory action and this, it is believed, is accomplished indirectly by its activation of profibrinolysin forming fibrinolysin.

It is also claimed that trypsin can be given orally to reduce inflammation and swelling if it is contained in an enteric tablet. Such a product is now available as Orenzyme (National Drug). These tablets contain both trypsin and chymotrypsin equivalent to the proteolytic activity of 20 mg. of crystalline trypsin. They are recommended in traumatic and other inflammations to reduce inflammation and edema. The initial dose is two tablets, four times daily.

Biological Products

Among the new biologicals introduced last year was Smallpox Vaccine Avianized (Lederle). This is produced by growing vaccinia virus on chick embryos rather than by inoculating calves. Not only is it easier to produce commercially but it is claimed to reduce the likelihood of local infection and scarring. Each immunization dose contains 0.26 mcg. of neomycin sulfate, 0.5 unit of polymyxin B sulfate, and 0.03 mcg. of tetracycline, and the virus is stabilized with sorbitol rather than glycerin.

The success of Lederle's avianized rabies vaccine in veterinary practice over the last several years has led to the testing of a similar product in humans. On the basis of preliminary tests, its use in humans looks quite promising and may replace the present products made by growing the virus in nerve or brain tissue. A product prepared by growing the virus on duck embryo is already marketed by Eli Lilly & Co.

A combination of adenovirus vaccine types 3, 4, and 7 and influenza virus vaccine adsorbed on aluminum phosphate is available as Resprogen Injection (Parke Davis). It is used for immunization against both of these virus diseases. Two injections of 1 cc. each two weeks apart are recommended.

A product for the combined immunization against diphtheria, tetanus, pertussis, and poliomyelitis (Tetravax—Merck Sharp & Dohme; Quadrigen—Parke Davis) announced in 1958 was released for general distribution in 1959. At the moment, the chances for an effective, safe oral vaccine against poliomyelitis look quite good. Sev-

eral such products are under very extensive controlled clinical testing. A number of advantages of an oral vaccine have been described. Since the vaccine produces an intestinal infection (usually asymptomatic), it results in the propagation and spread of this attenuated strain to other non-immunes thus protecting them against the disease without their active participation in the immunization program. It also eliminates the present hazard posed by those immunized with Salk vaccine. Such persons, while protected against paralytic polio, are not protected against an intestinal infection with a wild virus. If they become infected—although not ill—they become a silent source of infection to non-immunes.

The principal questions that must be answered definitively are the duration and degree of immunity conferred by the oral vaccine and, more importantly, whether repeated passages of the attenuated virus through humans will permit it to regain its original virulence. Some little evidence has been obtained that it does increase in its neurotoxicity but this may not be of significance since the test procedure used was extremely rigid (intraspinal inoculation in monkeys) and not believed by some to be a fair test.

Diagnostic Aids

The radiopaque compound, sodium diatrizoate, also used as the methylglucamine salt, is available in several forms ((Retrografin, Cholografin, Gastrografin, Duografin—Squibb). This last year, two new forms were released (Cardiografin—Squibb and Sinografin—Squibb). The former is an 85 per cent solution of diatrizoate methyl glucamine and is used in angiocardiography and aortography as a diagnostic aid in determining cardiac and congenital defects and acquired vascular disease. Sinografin is an aqueous solution containing both diatrizoate and iodipamide as the methylglucamines and is used in hysterosalpinography. Except in the hypersensitive patient, the drug is well-tolerated, diffuses readily, and is excreted from the circulation by the kidneys.

A dip and read test strip for the detection of phenylketonuria is available as Phenistix (Ames). They are cellulose strips impregnated with ferric and magnesium ions and cyclohexylsulfamic acid. The color reaction which takes place is between ferric ions and phenylpyruvate. The magnesium ions minimize interference by phosphates

and the cyclohexylsulfamic acid buffers the system for optimal color development.

Another dip and read test strip is Combistix Reagent Strips (Ames). These make possible the simultaneous determination of protein, glucose, and pH in a urine sample. Three areas on the test paper are separated by a water impervious barrier. The protein measuring area contains tetrabromphenol blue, a citrate buffer, and a protein adsorbent; the glucose area: glucose oxidase orthotolodin and a catalyst; the pH area: methyl red and bromthymol blue. All three measurements can be made in ten seconds using color standards for comparison.

A rapid slide test for the detection and quantitative determination of C-reactive protein is available (CR-Test—Hyland Laboratories) and another for the rapid estimation of gamma globulin levels (GG-Test—Hyland Laboratories.

Miscellaneous Products

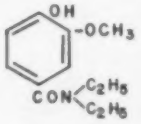
One of the EDTA series of chelating agents, edathamil disodium (Endrate Disodium—Abbott), is now supplied for use in pathologic calcifications and in the treatment of digitalis intoxication. In the latter, it acts by lowering the serum calcium level. It is given in a dose of 50 mg./Kg. diluted with 500 cc. of 5 per cent dextrose and administered by slow intravenous infusion (3 to 4 hours).

A new heparin antidote, hexadimethrine bromide (Polybrene—Abbott), appears to be a polymerized 1,5-dimethyl-1,5-diazundecamethylene methobromide. It is a strongly cationic agent and acts as does protamine to neutralize the strongly anionic heparin. The recommended dose is 1 mg. for each 100 units of heparin to be neutralized, and diluted so that the solution contains 1 mg./cc. Polybrene has a persistence of effect which prevents heparin rebound.

A new ultrashort barbiturate, methohexital, has been announced by Eli Lilly & Co. as under clinical trial. It is α-*dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid. It is not a thiobarbiturate but belongs to the N-methyl class which are also ultrashort in action since their Ka value is such that they exist chiefly in un-ionized form at physiological pH levels and are rapidly taken up by body fat. The compound has two asymmetric centers and four isomers are possible.

these were separated and the product selected (the α-*dl*) which seemed the best for anesthetic purposes.

Finally, a new barbiturate antidote, vanillic diethylamide, is under clinical study. It acts as a respiratory stimulant, deepening and



Vanillic diethylamide

slowing the respiration and helping restore blood pressure back to normal without marked increase in heart rate.

BOOK REVIEW

Drugs, Their Nature, Action and Use. Harry Beckman, xvii + 728 pp. W. B. Saunders Company, Phila., Pa., 1958.

As time passes, the scope of pharmacology increases. The vast amount of knowledge that exists with relation to drugs, their nature, actions, and uses, must be presented to the student in such a manner that it can be easily assimilated. As Dr. Beckman states, ". . . for the undergraduate medical student, who can devote but a fleeting moment in his career to prepare for the pharmacologic aspects . . . that lie ahead." This textbook has been written with the above thought in mind and, although not comprehensive, it does serve as an excellent supplement to laboratory and lecture material.

The subject matter is divided into three major sections. Section One is an introduction to pharmacology and an explanation of the role of the pharmacologist. Section Two deals with the nature of drugs, including their origin and history and some pharmacologic background. Also included in this section are chapters relating to the prescription, drug addiction, posology, factors affecting drug administration and the fate of drugs in the body. Section Three is the most comprehensive and is devoted to the actions and uses of drugs, including pharmacodynamics and practical applications. The drugs are classified according to their effects on the various systems of the body, such as muscle, blood, gastrointestinal, etc. Also included in this section are chapters dealing with drug use in specific symptoms and disease entities; enzymes, hormones, and vitamins; the pharmacology and use of radioactive compounds; and the pharmacology of drugs used as diagnostic aids.

This book makes for easy and enjoyable reading, and is highly recommended as a supplemental textbook for both pharmacy and medical school students.

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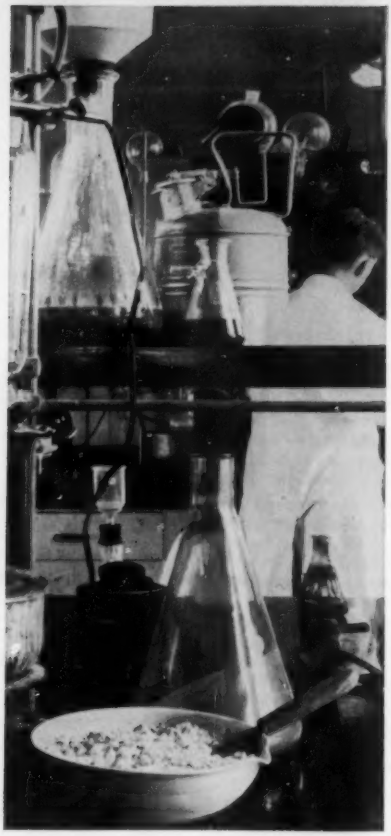

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